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Characterization of *Staphylococcus lugdunensis* endocarditis in patients with cardiac implantable electronic devices

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SUMMARY

Objectives: Although the application of cardiac implantable electronic devices (CIED) has greatly increased over the past few decades, CIED endocarditis is becoming a challenging scenario in clinical practice. Recently, *Staphylococcus lugdunensis* has emerged as a pathogen in CIED endocarditis. However, a detailed phenotypic characterization has not been addressed.

Methods: We conducted a systematic literature review covering the period between 1989 and 2011 using the PubMed, Medline, Cochrane, and Embase databases. All cases included had a CIED in use and met the modified Duke criteria for infective endocarditis, and all had isolates of *S. lugdunensis*. The clinical features, predisposing conditions, echocardiographic findings, and therapeutic strategies/outcomes were evaluated. Polymorphonuclear neutrophil functions were examined to test whether the defect of innate immunity may play a permissive role in host susceptibility to tissue destruction in *S. lugdunensis* endocarditis.

Results: Eleven patients with CIED endocarditis caused by *S. lugdunensis* were identified. Their mean age was 61.7 ± 11.2 years, and there was a male preponderance (72.7%). Six patients (54.5%) had undergone re-manipulation of the pacing system within a few months to years before the occurrence of clinical symptoms. The median time of symptoms before the diagnosis of CIED endocarditis was 60 days. On echocardiography, vegetations in the CIED were detected in nine cases (81.8%). Nine patients (81.8%) underwent surgical removal of the entire device, and one patient received medical treatment alone. The overall mortality rate was 18.2%. One patient had a septic perforation of the ventricular septum, with a high serum level of N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) in the absence of pump failure. The assessment of polymorphonuclear neutrophil (PMN) functions revealed normal PMN responses to the various stimuli and normal oxidative burst responses.

Conclusions: Identification and differentiation of staphylococcal species in a timely manner would allow us to intervene more aggressively at an earlier stage to prevent unfavorable outcomes. Clinicians should never consider the isolation of *S. lugdunensis* as contamination. In selected individuals, therapeutic abstention may be preferable to exposing patients to a high risk of *S. lugdunensis* CIED endocarditis due to re-manipulation of the pacing system. The prognostic value of NT-pro-BNP warrants further investigations.

1. Introduction

Although the application of cardiac implantable electronic devices (CIED) has greatly increased over the past few decades, the management of CIED endocarditis remains challenging. A wide variety of pathogens have been described, however *Staphylococcus lugdunensis*, a coagulase-negative Staphylococcus species (CoNS), has recently emerged because of its rapidly progressive, invasive nature in infective endocarditis. Infections with *S. lugdunensis* tend to have a more fulminant course, with a condition resembling that of *Staphylococcus aureus* infections rather than those caused by CoNS. Because a detailed phenotypic characterization of *S. lugdunensis* endocarditis in patients with CIED has not been addressed, we sought to analyze cases on this subject and to test whether the defect of innate immunity may play a permissive role in host susceptibility to tissue destruction in *S. lugdunensis* endocarditis.

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2. Case report

A 66-year-old woman presented to the emergency department (ED) with shortness of breath, hypotension, and delirium. Three years previously, a permanent pacemaker programmed in DDD mode had been implanted because of sick sinus syndrome with intermittent atrioventricular block. Two months prior to presentation she had undergone a pacing electrode repositioning for the dislodged atrial lead. In the past 2 weeks she had come to our ED twice because of intermittent low-grade fever, migratory arthralgia, and myalgia. On the first visit, the diagnostic workup was otherwise unrevealing and blood cultures grew CoNS, which were considered as skin contaminants. On the second visit, three sets of blood cultures were obtained and all yielded CoNS; none were regarded as pathogenic at that time. On admission, she had engorged jugular veins and a harsh holosystolic murmur at the left sternal border. Laboratory studies are shown in Table 1. An electrocardiogram showed atrioventricular sequential pacing with occasional premature ventricular complexes, and a chest radiograph revealed signs of pulmonary plethora. A newly-developed intracardiac shunt was observed (Figure 1); the right ventricle was of normal size and function and the left ventricular ejection fraction was 65%. Cardiac catheterization disclosed an elevated pulmonary artery pressure and a left-to-right interventricular shunting without significant coronary artery disease. Six sets of blood cultures grew CoNS isolates, further confirmed as *S. lugdunensis*. Intravenous antibiotics vancomycin and gentamicin were given, followed by successful removal of the entire pacemaker device using an excimer laser-assisted extraction technique. Microbiological analyses of the small vegetation adhering to the ventricular lead also yielded *S. lugdunensis*. Transvenous temporary pacing and intra-aortic balloon pump counterpulsation were introduced in order to maintain proper hemodynamics before a planned surgical repair. Unfortunately the patient died from sudden cardiac arrest 2 days later.

Table 1
Laboratory investigation on admission

Tests	Results	Reference
Hemoglobin	13.1 g/dl	12.2–14.7 g/dl
Leukocyte count	19.7×10^9/l	$4.5–11.0 \times 10^9$/l
Platelet count	88×10^9/l	$189–287 \times 10^9$/l
Blood urea nitrogen	87 mg/dl	8–25 mg/dl
Creatinine	1.2 mg/dl	0.7–1.5 mg/dl
Sodium	131 mmol/l	135–145 mmol/l
Potassium	4.1 mmol/l	3.3–4.9 mmol/l
Calcium, free	4.2 mg/dl	4.5–5.1 mg/dl
Uric acid	5.9 mg/dl	3–8 mg/dl
Creatine kinase	77 U/l	30–200 U/l
CRP	26.3 mg/dl	0–0.9 mg/dl
ALT	33 U/l	7–53 U/l
AST	41 U/l	11–47 U/l
Total cholesterol	196 mg/dl	<200 mg/dl
Triglycerides	167 mg/dl	<250 mg/dl
Homocysteine	6 μmol/l	4–12 μmol/l
Creatine kinase MB fraction	67 U/l	30–200 U/l 0–7 U/l
Troponin I	0.02 ng/ml	<0.05 ng/ml
D-Dimers	156 μg/l	0–200 μg/l
Fibrinogen	518 mg/dl	150–400 mg/dl
NT-pro-BNP	1933 pg/ml	<125 pg/ml
Arterial blood gas (room air)		
pH	7.43	7.35–7.45
pO_2	66.2 mmHg	80–105 mmHg
pCO_2	26.4 mmHg	35–45 mmHg
HCO_3^-	19.6 mmol/l	22–32 mmol/l

CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide.

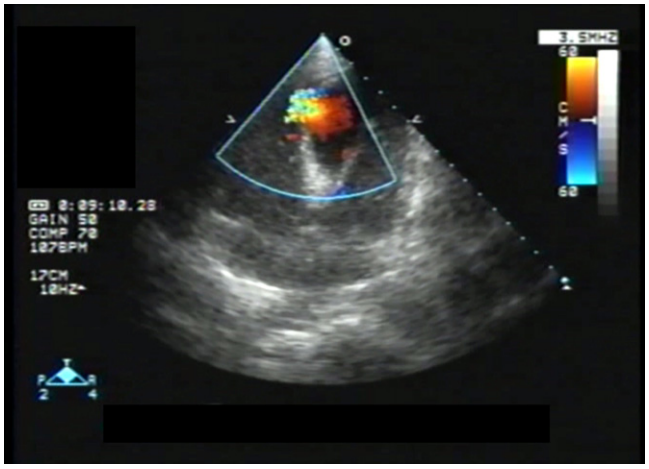

Figure 1. Doppler color flow mapping on transthoracic echocardiography showing a septic perforation of the interventricular septum (0.8 cm in diameter) with a measured pulmonary-to-systemic (Qp:Qs) flow ratio of 2.1:1.

3. Patients and methods

We conducted a systematic literature review covering the period between 1989 and 2011 using the PubMed, Medline, Cochrane, and Embase databases. All cases included in the review had a CIED in use and met the modified Duke criteria for infective endocarditis, and all had isolates of *S. lugdunensis*. The predisposing factors, echocardiographic manifestations, therapeutic strategies, and treatment outcomes were evaluated.

Polymorphonuclear neutrophil (PMN) functions were examined to determine whether the defect of innate immunity may play a permissive role in host susceptibility to tissue destruction in *S. lugdunensis* endocarditis. The PMN oxidative burst was measured by nitroblue tetrazolium reduction assay in the absence or presence of endotoxin (lipopolysaccharide from *Escherichia coli* 055:B5, 10 μg/ml for 15 min). PMNs primed with low doses of tumor necrosis factor alpha (TNF-α; 100 U/ml) and lipopolysaccharide (10 ng/ml) were then stimulated with formyl-methionyl-leucyl-phenylalanine and the oxidative burst was measured using oxidizing hydroethidine.[1] The expression of adhesion molecules (β_2-integrin, CD11b/CD18, and CD62L) on the cell surface of resting PMNs was also analyzed after stimulation with TNF-α and lipopolysaccharide.

4. Results

Eleven patients with CIED endocarditis caused by *S. lugdunensis* were identified (Table 2).[2–8] Their mean age was 61.7 ± 11.2 years, and there was a male preponderance (72.7%). Six patients (54.5%) had undergone re-manipulation of the pacing system within a few months to years prior to clinical symptoms. The associated conditions included type 2 diabetes mellitus (n = 2, 18.2%), cutaneous pocket/pulse generator infection (n = 4, 36.4%), hemodialysis (n = 1, 9.1%), and resection of kidney neoplasm (n = 1, 9.1%). The median duration of symptoms before the diagnosis of CIED endocarditis was 60 days. On echocardiography, vegetations in the CIED were detected in nine cases (81.8%). Nine patients (81.8%) underwent surgical removal of the entire device, and one patient received medical treatment alone. The overall mortality rate was 18.2%. One patient, as described above, had a septic perforation of the ventricular septum, with a high serum level of N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) in the absence of pump failure. The assessment of PMN functions demonstrated normal PMN responses to the various stimuli and normal oxidative burst responses.

Table 2
Cardiac implantable electronic device-related infective endocarditis caused by *Staphylococcus lugdunensis*

Case	Age/sex	Associated conditions	Duration of symptom before diagnosis	Echocardiographic findings	Treatment	Outcome/ complication	Ref.
1	F/68	Cutaneous infection 5 years earlier	3 weeks	13 × 12 mm peduncle vegetation on the wire	Penicillin and gentamicin (6 weeks); pacemaker removal by external traction	Recovered/ relapsing bacteremia 1 year later	2
2	F/68	Battery replacement 1 year earlier	≤12 months after manipulation	22 mm vegetation over the wire	Medical treatment (1 year); pacemaker removal by external traction	Recovered	3
3	M/66	None	>12 months after manipulation	23 mm vegetation over the wire	Cardiopulmonary bypass	Died	4
4	M/78	Battery replacement 4 months earlier, chronic pocket infection	≤12 months after manipulation	10 mm vegetation over the wire	Pacemaker removal by external traction	Recovered	4
5	M/63	Battery replacement 2 months earlier, chronic pocket infection	≤12 months after manipulation	8 mm vegetation over the wire	Pacemaker removal by external traction	Recovered	4
6	M/62	None	1 month	20 mm tricuspid vegetation and atrial lead vegetation	Cloxacillin and gentamicin; removal of pacemaker	Recovered	5
7	M/65	Diabetes mellitus, cutaneous extraction of a toenail	3 days	5 voluminous vegetations on the auricular and ventricular leads	Cloxacillin, gentamicin, and ofloxacin (8 weeks); pacemaker removal by thoracotomy	Recovered	5
8	M/41	Pulse generator infection 1 month earlier	1 month	Not available	Teicoplanin and fusidic acid (5 weeks), pristinamycin (4 months); pacemaker removal by thoracotomy	Recovered/ pulmonary embolism 4 days after surgery	6
9	M/61	Nephrectomy due to neoplasm of the left kidney	3 months	Thrombotic material over the ventricular pacemaker lead	Ampicillin/sulbactam and gentamicin (2 weeks); vancomycin and rifampin (3 weeks)	Recovered	7
10	M/41	Non-ischemic cardiomyopathy, diabetes mellitus, hemodialysis	A few days	36 mm × 21 mm,19 mm × 15 mm, and 17 mm × 4 mm vegetations attached to the right atrial and ventricular lead	Gentamicin and rifampin added to the vancomycin regimen (6 weeks); surgical extraction of the pacing apparatus	Recovered	8
11	F/66	Repositioning for dislodged atrial lead 2 months earlier	2 months	An apical ventricular septal defect	Vancomycin and gentamicin; pacemaker removal by excimer laser-assisted extraction	Died	Our patient

5. Discussion

Although most CoNS isolates from blood culture bottles are considered skin contaminants, some have been identified as important pathogens causing bloodstream infections. *S. lugdunensis*, initially described in 1988 as a separate species of CoNS, is an important emerging pathogen causing a wide variety of infections. Clinical observations have shown that *S. lugdunensis* tends to cause a fulminant infection such as infective endocarditis, and these infections are usually indistinguishable from those caused by *S. aureus*.[9] *S. lugdunensis* endocarditis generally responds poorly to conventional antimicrobial therapy alone, and this infection often results in rapid valvular destruction, myocardial abscess formation, and septic thromboembolism. Nevertheless, *S. lugdunensis* is often mistakenly thought to be a nonpathogenic cutaneous commensal, leading to high risk of mortality and morbidity.

While some virulence factors have been identified, the pathogenetic basis remains unclear. Studies have shown compelling evidence that *S. lugdunensis* can produce a thermostable DNase and express a fibrinogen-binding surface protein with considerable similarity to clumping factor A of *S. aureus*, which promotes bacterial adhesion to immobilized fibrinogen and interferes with opsonophagocytosis.[10] In addition, the production of enzymes that may act as invasion factors has been observed in *S. lugdunensis*, such as fatty acid modifying enzyme, esterase, protease, and lipase.[11] In fact, only about 25% of clinical isolates of *S. lugdunensis* produce extracellular slime, which has a role in bacterial colonization and interferes with the phagocytosis-associated activities of neutrophils. Therefore, the above-mentioned factors may not fully account for the tissue destruction capacity. To test whether the defect of innate immunity may play a permissive role in host susceptibility to tissue destruction in *S. lugdunensis* endocarditis, PMN function was examined in our patient, however the results were contrary to this pathogenetic hypothesis.

CIED-associated infection has increased considerably over the past decades, paralleled by the prevalence of its application in various types of dysrhythmia.[12] Several predisposing factors have been described, but in this case study we found that 54.5% of patients had undergone re-manipulation of the pacing system prior to CIED endocarditis. Conceivably, since not all cutaneous pocket/pulse generator infections are unequivocally in need of pacing wire removal and not all leads are indispensable for the patient's comfortable survival, therapeutic abstention may be preferable to exposing a patient to a high risk of CIED infection after re-manipulation of the pacing system.

The high serum level of NT-pro-BNP in our patient without pump failure is unusual. NT-pro-BNP, a 76-amino acid peptide, was co-secreted along with brain natriuretic peptide from the cardiac myocytes in response to excessive myocardial stretch and increased end-diastolic pressure/volume in the left ventricle. Plasma natriuretic peptide levels can significantly increase in patients with severe sepsis. Moreover, septic patients in intensive care units with echocardiographically proven preserved systolic function can have brain natriuretic peptide levels as high as those in patients with severe systolic pump failure. Of interest, a recent study showed that the level of serum NT-pro-BNP may be a valuable marker for predicting clinical outcomes in patients with infective endocarditis.[13] Although the dismal prognosis of our patient may plausibly reflect NT-pro-BNP as a useful surrogate for the risk stratification of patients with infective endocarditis, the

pathogenetic basis remains undefined and uncertainty exists as to whether sepsis-induced microcirculatory dysfunction or cytokine-mediated myocardial injury predominates.

In summary, the identification and differentiation of staphylococcal species in a timely manner would allow us to intervene more aggressively at an earlier stage to prevent unfavorable outcomes. Although less-appreciated, clinicians should never consider isolates of *S. lugdunensis* as contamination in CIED endocarditis. In selected individuals, therapeutic abstention may be preferable to exposing patients to a high risk of *S. lugdunensis* CIED endocarditis due to re-manipulation of the pacing system. The prognostic value of NT-pro-BNP warrants further investigations.

Conflict of interest: No conflict of interest to declare.

References

1. Elbim C, Prevot MH, Bouscarat F, Franzini E, Chollet-Martin S, Hakim J, et al. Polymorphonuclear neutrophils from human immunodeficiency virus-infected patients show enhanced activation, diminished fMLP-induced L-selectin shedding, and an impaired oxidative burst after cytokine priming. *Blood* 1994;**84**:2759–66.
2. Laguno M, Miró O, Font C, de la Sierra A. Pacemaker-related endocarditis. Report of 7 cases and review of the literature. *Cardiology* 1998;**90**:244–8.
3. Llinares P, Moure R, Cerqueiro J, Abalde M, Míguez E, Echaniz A, et al. Endocarditis caused by *Staphylococcus lugdunensis*. Hospital incidence. *Enferm Infecc Microbiol Clin* 1998;**16**:233–6.
4. Anguera I, Del Río A, Miró JM, Matínez-Lacasa X, Marco F, Gumá JR, et al. *Staphylococcus lugdunensis* infective endocarditis: description of 10 cases and analysis of native valve, prosthetic valve, and pacemaker lead endocarditis clinical profiles. *Heart* 2005;**91**:e10.
5. Bobin S, Durand-Dubief A, Bouhour D, Kirkorian G, Vandenesch F, Etienne J, et al. Pacemaker endocarditis due to *Staphylococcus lugdunensis*: report of two cases. *Clin Infect Dis* 1999;**28**:404–5.
6. Célard M, Lelièvre H, Obadia JF, Chevalier P, Forey F, Vandenesch F, et al. Long-standing bacteremia and endocarditis caused by *Staphylococcus lugdunensis* in a patient with an implantable cardioverter defibrillator. *Clin Microbiol Infect* 1997;**3**:387–8.
7. Seifert H, Oltmanns D, Becker K, Wisplinghoff H, von Eiff C. *Staphylococcus lugdunensis* pacemaker-related infection. *Emerg Infect Dis* 2005;**11**:1283–6.
8. Chopra A, Gulati D, Woldenberg N, Singh M. Intracardiac lead endocarditis due to *Staphylococcus lugdunensis*. *Int J Infect Dis* 2010;**14**:e291–3.
9. Zinkernagel AS, Zinkernagel MS, Elzi MV, Genoni M, Gubler J, Zbinden R, et al. Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. *Infection* 2008;**36**:314–21.
10. Geoghegan JA, Ganesh VK, Smeds E, Liang X, Höök M, Foster TJ. Molecular characterization of the interaction of staphylococcal microbial surface components recognizing adhesive matrix molecules (MSCRAMM) ClfA and Fbl with fibrinogen. *J Biol Chem* 2010;**285**:6208–16.
11. Von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. *Lancet Infect Dis* 2002;**2**:677–85.
12. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc* 2008;**83**:46–53.
13. Kahveci G, Bayrak F, Mutlu B, Bitigen A, Karaahmet T, Sonmez K, et al. Prognostic value of N-terminal pro-B-type natriuretic peptide in patients with active infective endocarditis. *Am J Cardiol* 2007;**99**:1429–33.